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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,257	10/07/2003	Joseph Loscalzo	102258.337US2	3120
7590 EDWARD D. GRIEFF Hale & Dorr L.L.P. 1455 Pennsylvania Ave, N.W. Washington, DC 20004			EXAMINER SRIVASTAVA, KAILASH C	
			ART UNIT 1657	PAPER NUMBER
			MAIL DATE 02/06/2008	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/679,257

Applicant(s)

LOSCALZO ET AL.

Examiner

Dr. Kailash C. Srivastava

Art Unit

1657

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 August 2007.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4,6-8 and 11-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4,6-8 and 11-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) ☐ Notice of Informal Patent Application |
| 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) ☐ Other: _____ |

DETAILED ACTION

1. Request for continued examination (i.e., RCE) under 37 CFR §1.114, including the fee set forth in 37 CFR §1.17(e), was filed in this application on 20 August 2007 after an Advisory Action was mailed on 20 July 2007 and a Final action mailed 26 March 2007. Since this application is eligible for continued examination under 37 CFR §1.114, and the fee set forth in 37 CFR §1.17(e) has been timely paid, the finality of the previous Office action mailed 26 March 2007 has been withdrawn pursuant to 37 CFR §1.114. Amendment and Response filed 20 August 2007 is acknowledged and has been entered. Accordingly an RCE has been established and the action on RCE follows.

2. The responses filed 20 August 2007 and 20 June 2007 are acknowledged and entered.

3. In view of remarks and amendment filed 20 June 2007 and remarks filed 20 August, the following rejection in the Office Action mailed 26 March 2007 is hereby withdrawn:

- obviousness rejection to Claims 1-2, 4 and 6-13 under 35 U.S.C. §103 (a) as obvious over combined teachings from Birch et al (U.S. Patent 5,627,191) in view of Cohn (U.S. Patent 4,868, 179) and further in view of Chobanian et al (U. S. Patent 5,645,839).

Claims Status

4. Claims 3, 5, 9 and 14-19 have been cancelled.

5. Claims 1-2, 4, 6-8 and 10-13 are pending and are examined on merits.

Information Disclosure Statement

6. The information disclosure statement filed 20 June 2007 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Rejections Under 35 U.S.C. § 103(a)

7. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

9. Claims 1, 2, 4, 6-8 and 11-13 are rejected under 35 U.S.C. § 103 (a) as obvious over combined teachings from Shapiro (U.S. Patent 5, 668,117) in view of Klemsdal et al. ((1994. A New Isosorbide Dinitrate Extended-Release Formulation: Pharmacokinetic and Clinical Parameters in Patients with Stable Angina Pectoris. Eur. J. Clin. Pharmacol., 47:351-354) with evidence from Wikipedia (Anonymous, Isosorbide mononitrate. From Wikipedia Pages 1-4 Printed 10/18/2007) and further in view of Chobanian et al (U. S. Patent 5,645,839).

Claims recite a sustained release transdermal patch comprising therapeutically effective amount of at least one anti oxidant and at least one of isosorbide dinitrate or isosorbide mononitrate, wherein isosorbide dinitrate is in range of 20 milligrams/ day to 200 milligrams/day. In said composition, the antioxidant is a hydralazine, ascorbic acid, beta carotene, tocopherol or Vitamin E, among others. Said composition further comprises a pharmaceutically acceptable carrier. In said composition, hydralazine compound is hydralazine hydrochloride, the isosorbide dinitrate is in range of 20 milligrms/ day to 200 milligrams/day and hydralazine hydrochloride in rang of 30 milligrams to 300 milligrams/day. Said composition further comprises a pharmaceutically acceptable carrier.

Regarding Claims 1, 2, 4 and 11, Shapiro teaches a composition comprising a transdermal patch, wherein said composition comprises an antioxidant (i.e., hydralazine) or isosorbide dinitrate (See Column 51, Lines 35-36, Line 66 and Column 52, Lines 3-6). Said composition comprises a dose in range of 3 milligrams/day to 300 mg/day of hydralazine and 20 milligrams/day to 240 milligrams/day of isosorbide dinitrate. Said composition also comprises other antioxidants, e.g., ascorbic acid, β -carotene, tocopherol or Vitamin E (e.g., Column 36, Lines 31-40. Note that Shapiro intrinsically teaches a transdermal patch

comprising same ingredients, i.e., antioxidant and isosorbide dinitrate, wherein antioxidants are same components (i.e., ascorbic acid, β -carotene, tocopherol or Vitamin E). Thus, the prior art composition explicitly and intrinsically teaches a transdermal patch on which are placed an antioxidant and isosorbide dinitrate, wherein antioxidants are from the group consisting of hydralazine ascorbate, β -carotene, tocopherol or Vitamin E as is instantly claimed because the prior art composition comprises the same components in same range of amounts as is instantly claimed (See e.g., *In re Best*, 195 USPQ 430, 433-CCPA 1977). Shapiro, however, does not teach a combination of the ingredients on the patch or a composition comprising an isosorbide mononitrate.

Klemsdal et al. teach similar effect of administering either isosorbide dinitrate or isosorbide mononitrate in treating angina pectoris (Figure 1). Furthermore, isosorbide mononitrate "exerts qualitatively similar effects" (See Wikipedia, Pages 1, Lines 36-37). Thus, one skilled in the art will be apprised to substitute isosorbide mononitrate for isosorbide dinitrate, or would even substantiate isosorbide dinitrate with isosorbide mononitrate.

Chobanian et al. teach a composition comprising a transdermal patch (Column 5, Lines 50-55) and at least one pharmaceutically acceptable carrier (Column 3, Lines 55-56). Chobanian et al. further teach additional anti oxidants (e.g., ascorbate, tocopherol and β -carotene; Column 4, Lines 63-64).

Thus, at the time, the claimed invention was made, an artisan of ordinary skill would have been motivated to combine the teachings from Shapiro according to beneficial teachings from Klemsdal et al., and Chobanian et al. to obtain a composition comprising a transdermal patch, at least one antioxidant and isosorbide dinitrate, wherein said antioxidant is one among: ascorbic acid, β -carotene, hydralazine hydrochloride, or tocopherol; because (i) Klemsdal et al teach that isosorbide mono nitrate and dinitrate produce the same qualitative effect and accordingly one may be substituted for the other and (ii) Chobanian et al. teach a composition comprising isosorbide dinitrate with a pharmaceutically acceptable carrier and a transdermal patch.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify teachings from Shapiro according to beneficial teachings from Klemsdal et al., and Chobanian et al. to obtain a sustained release transdermal patch comprising composition that is comprised of isosorbide dinitrate and/or mononitrate with hydralazine hydrochloride and one pharmaceutically acceptable carrier; because Klemsdal et al. teach isosorbide dinitrate may be substituted with isosorbide mononitrate and Chobanian et al teach a composition comprising isosorbide dinitrate in a pharmaceutically acceptable carrier and additionally a transdermal patch. Furthermore, the concentration

of isosorbide dinitrate and hydralazine hydrochloride disclosed in the prior art references is within the range that is instantly claimed. It is also *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." (*In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted)). In the instant case, *In re Kerkhoven* is applicable because the prior art teaches a composition comprising each of the elements (i.e., anti oxidant, wherein anti oxidant comprises ascorbic acid, β -carotene, hydralazine hydrochloride, tocopherol and Vitamin E; transdermal patch and isosorbide dinitrate).

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

10. For reasons aforementioned, no Claims are allowed.

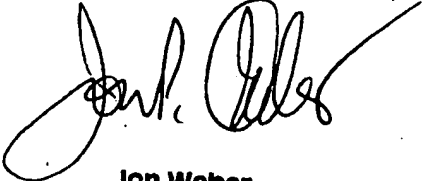
11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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24 October 2007


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